American Chemistry Council Good Chemistry Makes It Possible

May 24, 2005

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Ms. Cynthia Oshita
Office of Environmental Health Hazard Assessment
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Sacramento, CA 95812-4010

Dear Ms. Oshita:

The American Chemistry Council Phthalate Esters Panel (Panel) submits these comments in response to the California Office of Environmental Health Hazard Assessment (OEHHA) Notice of Intent to List Chemicals of March 4, 2005. The Panel includes the major U.S. producers and some processors of phthalate esters. These comments pertain to the four phthalates for which OEHHA provided notice that it intends to list as chemicals known to the state to cause reproductive toxicity under the Authoritative Bodies Mechanism of Proposition 65 – dibutyl phthalate (DBP), butyl benzyl phthalate (BBP), di-n-hexyl phthalate (DnHP), and diisodecyl phthalate (DIDP). These comments will show that these four phthalates fail to meet the listing criteria of Proposition 65.

The Panel renews in whole the comments it submitted to OEHHA on August 26, 2004. These comments reiterate and expand upon those earlier comments, and address some of OEHHA's responses to those comments. These comments make the following points: 1) The marmoset is a scientifically sound model for investigating potential effects of phthalates on human reproduction, as pointed out in the Panel's previous comments, and OEHHA's responses to those comments are inadequate to disqualify the marmoset as such a model; 2) the marmoset data comprise scientifically valid data, not considered by NTP-CERHR, which establish that the phthalates do not meet the criteria for identification "as causing reproductive toxicity;" 3) NTP-CERHR found minimal to negligible risk of human reproductive toxicity and, therefore, the Proposition 65 listing criteria are not met for these phthalates; and 4) OEHHA has no statutory mandate to list chemicals such as these phthalates, which pose no significant risk to public health, and the Panel believes it would be poor public policy to list such low-risk chemicals under Proposition 65.

For the reasons given in these comments, and in its earlier comments, the Panel believes that DBP, BBP, DnHP and DIDP do not meet the criteria for listing under Proposition 65 pursuant to the authoritative bodies mechanism, and that OEHHA should not list these four phthalates under Proposition 65.

If you have any questions, please call Marian K. Stanley, Manager of the Phthalate Esters Panel, at (703) 741-5623 or email her at Marian_Stanley@americanchemistry.com.

Sincerely yours,

Courtney M. Price

Courtney M. Price
Vice President, CHEMSTAR

Enclosure

Before the
California Environmental Protection Agency
Office of Environmental Health Hazard Assessment

**COMMENTS OF THE
PHTHALATE ESTERS PANEL OF THE AMERICAN CHEMISTRY COUNCIL
ON NOTICE OF INTENT TO LIST CHEMICALS**

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Notice of Intent to List Chemicals	)
California Regulatory Notice Register 05, No. 9-Z,	)
pp. 289-290 (March 4, 2005)	)
	)

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EXECUTIVE SUMMARY

The American Chemistry Council Phthalate Esters Panel (Panel) submits these comments in response to the California Office of Environmental Health Hazard Assessment (OEHHA) Notice of Intent to List Chemicals of March 4, 2005 (California Regulatory Notice Register 05, No. 9-Z, pp. 289-290 (March 4, 2005)). The Panel includes the major U.S. producers and some processors of phthalate esters. These comments reiterate and expand upon the Panel's comments of August 26, 2004, which were submitted in response to OEHHA's May 28, 2004 Request for Information on Chemicals Under Consideration for Possible Listing via the Authoritative Bodies Mechanism. In addition, these comments address portions of OEHHA's response to those earlier comments, contained in a March 1, 2005 letter from Dr. George V. Alexeeff, OEHHA Deputy Director of Scientific Affairs, to Ms. Courtney M. Price, Vice President of CHEMSTAR. These comments pertain to the four phthalates for which OEHHA has provided notice that it intends to list as chemicals known to the state to cause reproductive toxicity under the Authoritative Bodies Mechanism of Proposition 65 – dibutyl phthalate (DBP), butyl benzyl phthalate (BBP), di-n-hexyl phthalate (DnHP), and diisodecyl phthalate (DIDP). For the reasons presented in both the August 2004 comments and these comments, the Panel strongly believes that these phthalates should not be listed under Proposition 65. These comments renew in whole the comments submitted by the Panel in August 2004, and make the following points:

- OEHHA's responses to the Panel's earlier comments that new marmoset data strongly suggest the effects observed in rodents are not relevant to humans are not sufficient to invalidate the marmoset as a model for investigating the potential effects of phthalates on human reproduction. In general, a primate is considered to be a more relevant species than rats for human risk assessment, since humans are themselves primates.

- OEHHA's stated basis for listing these phthalates under the Authoritative Bodies Mechanism is the monographs published in 2003 by the National Toxicology Program Center for the Evaluation of Risks to Human Reproduction (NTP-CERHR). OEHHA acknowledged in its response that the marmoset data were "relevant for DBP, BBP, DnHP, and DIDP" and thus considered by OEHHA to be "'new data' that were not considered by the authoritative body." Because the marmoset data were not considered by the authoritative body (NTP-CERHR), and those data clearly establish that the association between adverse reproductive effects in humans and the phthalates is not "biologically plausible," these four phthalates fail to meet the listing criteria of Proposition 65.

- In its representation of NTP-CERHR's conclusions, OEHHA fails to acknowledge that NTP-CERHR found minimal to negligible risk of human reproductive toxicity for these phthalates. Because NTP-CERHR did not clearly conclude that the phthalates cause reproductive toxicity in humans, the Proposition 65 listing criteria are not met for these four phthalates.

- OEHHA has no statutory mandate to list chemicals such as these phthalates, which pose no significant risk to public health. Therefore, listing these phthalates under Proposition

65 makes little sense from a public policy perspective, as it would likely to lead to public and regulatory concern about these substances that is not warranted in light of the data for them. Proposition 65 listing also is likely to lead to reformulation of products away from the listed phthalates, and toward other chemicals about which less reproductive toxicity information may be known. The Panel strongly believes that sound public policy would avoid promoting such consequences through Proposition 65 listing, where human exposures to substances – such as DBP, BBP DnHP and DIDP – have been shown to pose a very low risk of reproductive or developmental toxicity.

The Panel believes that DBP, BBP, DnHP and DIDP do not meet the criteria for listing under Proposition 65 pursuant to the authoritative bodies mechanism, and that in any event would be poor public policy to list such low-risk chemicals. Therefore, OEHHA should not list these four phthalates under Proposition 65.

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INTRODUCTION

The American Chemistry Council Phthalate Esters Panel (Panel) submits these comments in response to the California Office of Environmental Health Hazard Assessment (OEHHA) Notice of Intent to List Chemicals of March 4, 2005.[1] The Panel includes the major U.S. producers and some processors of phthalate esters.[2] These comments pertain to the four phthalates that OEHHA has stated it intends to list as chemicals known to the state to cause reproductive toxicity under the Authoritative Bodies Mechanism of Proposition 65[3] – dibutyl phthalate (DBP), butyl benzyl phthalate (BBP), di-n-hexyl phthalate (DnHP), and diisodecyl phthalate (DIDP). OEHHA states that the basis for these listings is the monographs published in 2003 by the National Toxicology Program Center for the Evaluation of Risks to Human Reproduction (NTP-CERHR, 2003a,b,c,d).

At the outset, the Panel reaffirms in whole its August 26, 2004 comments, which were submitted in response to OEHHA's May 28, 2004 Request for Information on Chemicals Under Consideration for Possible Listing via the Authoritative Bodies Mechanism.[4] In addition, these comments reiterate and expand upon the Panel's earlier comments, and address portions of OEHHA's response to those earlier comments, which are contained in a March 1, 2005 letter from Dr. George V. Alexeeff, OEHHA Deputy Director of Scientific Affairs, to Ms. Courtney M. Price, Vice President of CHEMSTAR.

Part I of these comments addresses OEHHA's responses to the Panel's previous submission of marmoset data (not considered by NTP-CERHR), which strongly suggest that the effects of phthalates observed in rodents are not relevant to humans. In its response, OEHHA listed four features of marmoset reproductive physiology, based upon which it concluded that the marmoset is not a suitable model for evaluating the potential reproductive effects of phthalates on humans. Because these features have not been shown to be relevant to the mechanism by which phthalates affect reproduction in the species most sensitive to phthalate perturbation (i.e. rodents), and do not appear to interfere with other phthalate effects known to manifest in marmosets (e.g., liver enzyme induction), they do not invalidate the marmoset as a model for investigating the potential effects of phthalates on human reproduction. The Panel continues to believe that the marmoset data strongly suggest that phthalates do not pose a reproductive toxicity hazard for humans.

OEHHA acknowledges in its response that the marmoset data were "relevant for DBP, BBP, DnHP, and DIDP" and thus considered by OEHHA to be "'new data' that were not considered by the authoritative body." Part II of these comments explains that, because the marmoset data were not considered by the authoritative body (NTP-CERHR), and those data

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1 California Regulatory Notice Register 05, No. 9-Z, pp. 289-290 (March 4, 2005); http://www.oehha.ca.gov/prop65/CRNR_notices/admin_listing/intent_to_list/noilpkg21.html.

2 The Panel's members include BASF Corporation, Eastman Chemical Corporation, ExxonMobil Chemical Company, Ferro Corporation, and Teknor Apex Company.

3 *See* CAL. HEALTH & SAFETY CODE § 25249.8(b); CAL. CODE REGS. tit. 22, § 12306.

4 http://www.oehha.ca.gov/prop65/CRNR_notices/admin_listing/requests_info/dcallin21.html#get.

clearly establish that the association between adverse reproductive effects in humans and the phthalates is not "biologically plausible," these four phthalates fail to meet the listing criteria of Proposition 65.

Part III of these comments points out that, even assuming that the rodent data cited by NTP-CERHR and relied upon by OEHHA are relevant to humans, NTP-CERHR generally found that these phthalates posed minimal to negligible risk of reproductive or developmental effects in humans. Nevertheless, in its representation of NTP-CERHR's conclusions, OEHHA fails to acknowledge qualifying language, the result of which is an overstatement of NTP-CERHR's findings of phthalate reproductive toxicity. Because NTP-CERHR did not clearly conclude that the phthalates cause reproductive toxicity, the Proposition 65 listing criteria are not met for these four phthalates.

Part IV of these comments makes the point that OEHHA has no statutory mandate to list chemicals such as these phthalates, which pose no significant risk to public health. Therefore, the Panel believes that listing these phthalates under Proposition 65 makes little sense from a public policy perspective as it would likely to lead to public and regulatory concern about these substances that is not warranted in light of the data for them, and would also likely lead to reformulation of products away from the listed phthalates, and toward other chemicals about which less reproductive toxicity information may be known.

For the reasons given in these comments, and in its August 2004 comments, the Panel believes that DBP, BBP, DnHP and DIDP do not meet the criteria for listing under Proposition 65 pursuant to the authoritative bodies mechanism, and that in any event would be poor public policy to list such low-risk chemicals. Therefore, OEHHA should not list these four phthalates under Proposition 65.

I. OEHHA'S RESPONSES TO THE PANEL'S EARLIER COMMENTS ARE NOT SUFFICIENT TO INVALIDATE THE MARMOSET AS A SUITABLE MODEL OF HUMAN REPRODUCTIVE PHYSIOLOGY

A. The Features of Marmoset Reproductive Physiology Listed by OEHHA in its Response Letter Are Insufficient to Invalidate the Marmoset as a Model for Investigating the Potential Effects of Phthalates on Human Reproduction

In its August 26, 2004 comments, the Panel stressed that a recent study on marmosets (MCSI, 2003; Tomonari, 2004), which had not been evaluated by NTP-CERHR, strongly suggests that DEHP and other phthalates do not pose a reproductive toxicity hazard for humans. This study demonstrated that daily administration of 2500 mg DEHP/kg/day from weaning through maturity did not affect male reproductive tract development in the marmoset. In its response to this comment, OEHHA stated:

> OEHHA agrees with [the Panel] that these data are relevant for DBP, BBP, DnHP, and DIDP. . .and thus considers this study as "new data" that were not considered by the authoritative body.

However, OEHHA then listed four features of marmoset male reproductive physiology, based upon which it concluded that the marmoset is not a suitable species for investigating potential reproductive effects of DEHP (and by implication other phthalates) in humans. The comments below demonstrate that these four features of marmoset reproductive physiology do not invalidate the marmoset as a model for investigating potential human reproductive effects of phthalates.

Initially, it is reasonable to presume that unique features of any non-human animal model can be cited that might affect the comparison of that model to humans. For example:

- rhesus macaque males display seasonal variation in gonadal function and testosterone production that is not mirrored in humans, marmosets or rats;
- macaques exhibit very low levels of inhibin B neonatally, relative to rats and humans; and
- rats and macaques show a segmental/radial distribution of stages of spermatogenesis within the testis, while humans and marmoset exhibit a semi-helical organization (Sharpe, et al., 2000).

Because all animal models will be different from humans in some respects, merely pointing out those differences does not provide justification sufficient to reject a particular model. Rather, it is critical to determine whether the differences between the animal model and humans are pertinent to the specific comparison, which in turn depends on whether the mechanism that produces the effects of a given compound is relevant to the particular species differences described. Absent strong evidence to the contrary, a primate is considered to be a more relevant species than rats for human risk assessment, since humans are themselves primates.

With this in mind, what follows is an examination of the four features of marmoset reproductive physiology cited by OEHHA in its response to the Panel's comments, and an analysis of whether the differences between marmoset and human male reproductive physiology are pertinent to a determination of whether the marmoset is a valid model of human male reproduction. This analysis shows that there is no evidence that the features of marmoset reproductive physiology listed in OEHHA's response letter are related to the mechanism by which DEHP, or other phthalates, affect male reproduction. This analysis (and that of Section I.B.) is based on a review of relevant research by Dr. Suzette Tardif, Associate Director of the Southwest Foundation for Biomedical Research, who is a leading authority on marmoset reproduction.[5]

1. Marmoset Sertoli Cell Morphological Uniformity Does Not Invalidate the Marmoset as a Model for Human Reproductive Toxicity

OEHHA's Response 1 to Comment 1: "*There is no morphological variation in the spermatogenic epithelium . . . [indicating that] marmosets are totally different from most other mammals studied, including rodents and humans*."

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5 Dr. Tardif's comments reflect her opinions and are not to be interpreted as necessarily the opinions of the Southwest Foundation for Biomedical Research.

This statement appears to be based on the conclusions of Rune, et al. (1992) that there was no indication of "a dependent relationship between the spermatogenic stages and Sertoli cell morphology" and that "[a]s far as this finding is concerned, marmoset Sertoli cells differ from those of other species." While Sertoli cells appear to be an initial target of DEHP (and MEHP) in rodents, there is no evidence that this difference (Sertoli cell morphological uniformity) is in any way related to the mechanism by which DEHP affects the Sertoli cells. In fact, despite this difference, Rune, et al. conclude that, because marmoset Sertoli cells appear and behave similarly in vitro and in vivo, "the adult marmoset monkey could provide a primate model for mature Sertoli cells in culture, since there is [also] a close similarity to human adult Sertoli cells in vitro and in vivo."

2. **The Marmoset's Pituitary Production of Chorionic Gonadotropin, Rather Than Luteinizing Hormone Does Not Invalidate the Marmoset as a Model for Human Reproductive Toxicity**

> OEHHA's Response 2 to Comment 1: *[T]he pituitary of common marmosets does not produce [luteinizing hormone] LH. Instead, it produces chorionic gonadotropin (CG), which is only produced in the placenta of humans or rodents. . . ."*

The evidence does support the conclusion that the primary luteotrophic gonadotropin produced by the marmoset pituitary is CG, and not LH. However, this distinction may be inconsequential, as both CG and LH bind to the same receptors and CG essentially acts like LH in tissues such as the luteal cells of the ovary. Whether the difference in molecular structure of the pituitary gonadotropin is significant is unknown, and will depend upon the phthalates' not yet established mechanism of action. On the other hand, it is clear that the basic hypothalamic-pituitary-gonad control mechanisms present in other primates are also present in marmosets. For example, release of pituitary gonadotropins and, subsequently, of testosterone production in male marmosets are affected by GnRH analogues in a fashion identical to that of other primates, including humans (e.g., Prince, et al., 1998).

3. **The Inability to Co-Transplant Marmoset and Hamster Testicular Tissue into Nude Mice Does Not Invalidate the Marmoset as a Model for Human Reproductive Toxicity**

> OEHHA's Response 3 to Comment 1: *"Recent studies using transplanting techniques have shown that the conditions needed for initiation of spermatogenesis in the marmoset are remarkably different from those present in other mammals."*

This comment appears to be based on the work of Wistuba et al. (2004) in which the authors co-grafted marmoset and hamster testicular tissue into nude mice, but were unable to get marmoset spermatogenesis to proceed beyond the spermatogonial stage. The failure of the grafting techniques described by Wistuba et al. is likely related to Response No. 2 above, i.e., the difference in gonadotropin structure in New World monkeys, such as marmosets, compared to Old World monkeys and rodents. Witsuba et al. acknowledge that although they attempted to circumvent this difference by administering human CG to the host hamsters, "it might be that the exogenous administration was not sufficient to achieve a microenvironment in the mouse recipient that mimics the situation in the marmoset." This hypothesis would best be tested by attempting a similar grafting with testicular tissue from another New World monkey, such as a squirrel monkey, since all New World monkeys are thought to share the same LH receptor changes that likely drive the difference in pituitary gonadotropin. Such an experiment has not yet been attempted, and until is has been, no valid basis exists to conclude that the failed transplant experiments of Wistuba et al. indicate that marmosets are not a suitable human reproductive model.

4. Marmoset Twin Germ Cells Likely Are Not Chimeric, and Therefore Marmoset Chimerism Does Not Invalidate the Marmoset as a Model for Human Reproductive Toxicity

OEHHA's Response 4 to Comment 1: *"XX germ cells have been reported from the testes of male marmosets with a female twin . . . [t]he chimeric feature of [marmoset] twins is rare in most mammals including rodents and humans. . . ."*

The chimeric nature of marmoset twin germ cells cited by OEHHA appears to be based on two older studies, Benirschke and Brownhill (1963) and Hampton (1973). However, the results of these older studies have not been replicated and OEHHA acknowledged in its response letter that the occurrence of germ cell chimeras in marmosets has been questioned (e.g., Ford and Evans, 1977) and that more study is needed to clarify this issue. Indeed, most investigators working with marmosets today agree that it is highly unlikely that germ cell chimerism occurs in marmosets (Gengozian et al., 1980; Ford and Evans, 1997). Moreover, given the presence of hematopoietic cells (which are known to be chimeric) in most marmoset tissues, it is difficult to definitively demonstrate that chimerism occurs in germ cells as opposed to supporting hematopoietic cells within the gonad. Consequently, this purported difference between marmosets and other mammals is unverified and should not be relied upon to conclude that marmosets are not a viable model for human reproduction studies.

B. The Conclusions of Zuhkle and Weinbauer Regarding the Use of Marmosets as a Model for Human Reproductive Toxicity are Incorrect, and Possibly Biased

OEHHA's Response: *"Because of the fundamental differences in the testis between common marmosets and humans, it has recently been suggested that 'the use of this animal model cannot be recommended for reproductive toxicology assessment' (Zuhkle and Weinbauer, 2003)."*

Most of the points raised in Zuhkle and Weinbauer (2003) are the same as those enumerated by OEHHA in Responses 1 – 4 above. Some of the additional points raised by the authors (i.e., that high interindividual fluctuations of steroid hormone levels makes monitoring of ovarian cycle based upon serum concentrations difficult or not feasible; and that marmosets require a complex diet in captivity) are simply incorrect. In relation to the ability to monitor ovarian cyclicity based on serum hormone concentrations, numerous studies have used circulating estradiol and progesterone concentrations to track ovarian cyclicity, so this is not an issue.

Moreover, the U.S. Food and Drug Administration (FDA), one of the five authoritative bodies specifically identified in Proposition 65 for the purposes of identifying chemicals as causing reproductive toxicity,[6] has proposed that the marmoset is an appropriate model for human health assessment, and may be a more appropriate model than the rat for evaluation of reproductive toxicity hazard to humans. For example, the FDA Safety Assessment of DEHP states that:

> Spermatogenesis in the marmoset is organizationally similar to the process that occurs in humans, with regard to length of the spermatogenic cycle, duration of spermatogenesis, and number of mitotic divisions (Millar et al., 2000; Weinbauer et al., 2001). Consequently, the marmoset has been described as an appropriate model for experimental studies of human spermatogenesis. By analogy, it can be assumed that DEHP-induced effects on this process seen in marmosets would be applicable for humans.

(FDA, 2001, p. 35.)

Finally, there is a possibility of bias of Zuhkle and Weinbauer in favor of the cynomolgus macaque as a model for reproductive toxicology, given that both authors work for Covance, a company that sells cynomolgus macaques (but not marmosets) to pharmaceutical firms and biomedical institutions.

C. Vitamin C Levels in the Marmoset Do Not Negate the Relevance of the Marmoset Study to Human Risk Assessment

OEHHA's Response: *"[V]itamins C and E are protective against the testicular effects of DEHP in rats or mice (Ishihara et al., 2000; Ablake et al., 2004). Common marmosets require high levels of dietary vitamin C so regular diets for this species usually contain high levels of vitamin C supplements (e.g., MCSI, 2003). Serum levels of vitamin C in common marmosets are markedly higher (2.56 mg/100ml in average; Flurer and Zucker, 1987; 1989) than most other mammals (0.63 mg/100ml in average in humans; Hampl et al., 2004), suggesting a possibility of reduced sensitivity to DEHP in this species."*

As indicated by the above response, OEHHA is concerned that the lack of observed effects of DEHP on marmoset reproduction (e.g., MCSI, 2003; Tomonari et al., 2004) may be due to the protective action of high doses of vitamin C, rather than a difference in the effects of DEHP between rodents and primates. These concerns, however, are not well founded because: 1) the levels of vitamin C used in Tomonari et al. (2004) are not high relative to the marmoset's requirements and 2) based on the available science (discussed below), it is not clear that vitamin C affords any protection to primates from DEHP exposure. Moreover, if the level of vitamin C in the marmosets' diet in Tomonari et al. in fact provided the degree of protection necessary to be responsible for the observed lack of effects at doses of 2500 mg/kg/day, then the level of vitamin C in the average human diet would be protective of similar exposures to DEHP (test exposures were more than 100,000-fold higher than CDC data demonstrate actually occur in humans). In other words, the vitamin C levels in the marmoset diet in the Tomonari et al. study

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[6] CAL. CODE REGS. tit. 22, § 12306(i)(5).

were similar to normal levels in the human diet and, consequently, whether vitamin C had a protective effect is not directly relevant to a risk assessment.

Marmosets, like all primates, require that their diet be supplemented with vitamin C (ascorbic acid) (NRC, 2003). Flurer et al. (1987) reported that marmosets need more vitamin C than do humans, suggesting that a minimum of 20 mg/kg/day (the same amount cited by NRC, 2003) should be provided in the diet. Flurer et al. also stated that they consider the optimal vitamin C content in the diet of the marmoset to be 2,000 ppm. The diet used in Tomonari et al. provided 1g vitamin C per 1,000 g feed (0.1%, or 1,000 ppm, or about 80 mg/day), an amount recommended in the published literature (Layne and Power, 2003), and only one-half that recommended by Flurer et al. Thus, the amount of vitamin C used in the Tomonari et al. study was not excessive relative to the marmoset's dietary requirements and any potential protection conferred by the vitamin C would not be out of line with the degree of protection afforded the marmoset by its natural diet.

Moreover, it is not clear whether a vitamin C-supplemented diet even impacts DEHP-induced testicular effects. Ishihara et al. (2000) demonstrated that rats given vitamins C and E in drinking water (about 450-500 mg/kg/day vitamin C) exhibited reduced testicular effects, relative to animals not receiving vitamins, from exposure to 20,000 ppm (1,000 – 1,500 mg/kg/day) DEHP in the diet. The absolute testes weights of DEHP/vitamin treated animals were significantly lower than controls (although testes-to-body weight ratios were comparable to controls), but significantly higher than DEHP-exposed rats that did not receive vitamins C and E. In addition, testicular pathology of DEHP/vitamin rats was improved relative to DEHP rats, though not entirely normal (spermatogenesis was present, but not at control levels; severe aspermatogenesis was not observed in DEHP/vitamin animals). Thus, the combination of vitamins C and E afforded some protection to the rats against the reproductive toxicity of high doses of DEHP to rats.

Similarly, in Ablake et al. (2004), CD-1 male mice were fed a diet containing 2% DEHP for 15 days and then fed a DEHP-free diet with or without supplementation of 3.0 mg/mL vitamin C and 1.5 mg/ML vitamin E in drinking water for another 50 days. The results showed that the DEHP-treatment induced aspermatogenesis, but that the damaged seminiferous epithelium spontaneously recovered whether the vitamins were provided or not, indicating that the DEHP-induced aspermatogenesis was reversible. In addition, the supplementation of vitamins C and E in the diet significantly accelerated regeneration of the injured seminiferous epithelium, suggesting that the vitamins have a therapeutic effect on DEHP-induced aspermatogenesis.

However, the potential protective effect of vitamin C in Ishitara et al. and Ablake et al. cannot be distinguished from that of vitamin E because, in both studies, the two vitamins were provided together. Verma and Nair (2001) showed that mice pretreated with vitamin E showed little or no signs of testicular toxicity following treatment with aflatoxin. On the other hand, Cave and Foster (1990) reported that very high levels of vitamin C (2 mM) were required for any protective effect against *m*-dinitrobenzene or *m*-nitrosonitrobenzene toxicity on Sertoli cells *in vitro*. Hence, it is possible that vitamin C had little impact on testicular toxicity, and that vitamin E played the larger role in the protective effect observed by Ishihara et al. in rats and Ablake et al. in mice.

Even if vitamin C does protect rats and mice against the effects of DEHP exposure, because rodents produce their own vitamin C the protective effect of dietary vitamin C in primates would have to be much greater than in rodents to account for the results of Tomonari et al. For example, since rats produce about 150 mg/kg/day of their own vitamin C (Chatterjee, 1973), the rats in the Ishihara et al. study were effectively exposed to a total vitamin C dose of about 600 – 650 mg/kg/day. Comparing the results of Ishihara et al. to Tomonari et al., rats given about 600 mg/kg vitamin C (plus 225 mg/kg vitamin E) exhibited smaller testes and reduced spermatogenesis after exposure to 1,000 mg/kg/day DEHP whereas marmosets given only about 360 mg/kg/day vitamin C had normal-sized testes and comparable spermatogenesis to controls (based on sperm counts) when ingesting 2,500 mg/kg/day DEHP. Thus, if the hypothesis is that dietary vitamin C accounted for the lack of effects seen in Tomonari et al., as opposed to a difference in the marmosets' sensitivity to DEHP, then a much smaller dose of vitamin C (50 – 66% of the amount given to the rats) would have to have protected the marmosets against 2 – 2.5 times the amount of DEHP given to rats. Put another way, vitamin C would have to be about 3 – 5 times more protective in primates than rodents to account for the results of Tomonari et al.

Indeed, if such a small amount of vitamin C in the diet had a complete protective effect against the high doses of DEHP given the marmosets, one might question the possible impact of DEHP exposure on human health. The RDA for vitamin C is 75 mg/person/day for women and 90 mg/person/day for men (NRC, 2003), although the mean daily intake is about 100 mg/day based on NHANES III and CSF II surveys (NRC, 2003). If 80 mg/day was as protective to primates as suggested, then the risk to humans would appear quite low since human exposures to DEHP are at least 100,000 times lower than the amount received by the marmosets (McKee et al., 2004), and the human diet contains higher levels of vitamin C. Even if one were to calculate the protective potential of that much vitamin C on a mg/kg body weight basis, the 360 mg/kg/day dose of vitamin C (hypothetically) protected the marmosets from testicular effects at 2,500 mg/kg DEHP (roughly a 7-fold protection factor). Applying this protection factor to an average human intake of 1.3 – 1.4 mg/kg/day vitamin C (90 – 100 mg/day for a 70 kg person), humans would be at no risk of testicular effects from DEHP exposures up to 6 mg/kg/day or roughly 10,000 times the mean exposures as determined by the CDC (Blount et al., 2000; CDC, 2001; CDC, 2003).

Thus, it seems unlikely that the amount of vitamin C provided the marmosets in Tomonari et al. invalidates the study's findings of no effect. Further, even if vitamin C had a protective effect, it is unlikely that any human other than one severely deficient in vitamin C would be at risk of adverse effects from exposure to the amounts of DEHP found in the environment.

In addition, contrary to OEHHA's statement that "[s]erum levels of vitamin C in common marmosets are markedly higher (2.56 mg/100 ml in average; Flurer and Zucker, 1987; 1989) than most other mammals (0.63 mg/100ml in average in humans; Hampl et al., 2004)," human and marmoset serum levels of vitamin C are not that different. Hampl et al. (2004) indicate that mean vitamin C levels in human plasma range from about 0.64 mg/dL (36.3 μM) to 0.97 mg/dL (55 μM), with an average of about 0.8 mg/dL (44 μM). The serum vitamin C level of 2.6 mg/dL cited as "average" by OEHHA is derived from marmosets that were given 2,000 ppm dietary vitamin C (Flurer et al., 1987). This level is four times the minimum requirement cited by Flurer et al., and twice the recommended level of Layne and Power (2003). The marmosets in the Tomonari DEHP study were fed only 1,000 ppm vitamin C, with no reported vitamin C-related ill effects. Visual inspection of the Figure 2 in the Flurer et al. study (1987) indicates that, for marmosets, a 1,000 ppm diet results in a plasma vitamin C level of about 1.9 mg/dL. Therefore, it is equally, if not more, appropriate to conclude that average marmoset serum vitamin C levels are about 1.9 mg/DL, which is only a 2-fold difference from humans, not 4-fold as indicated by OEHHA. Even this small difference may not be statistically significant as the HPLC methodology used by the two different groups of investigators incorporated different detection systems, electrochemical detection (Hampl et al., 2005) and spectrophotometry (Flurer et al., 1987).

In any event, intracellular levels, not plasma levels, are probably responsible for any protective effect that vitamin C may afford. Intracellular ascorbate levels are about 100-fold greater than those found in plasma (Tsukaguchi et al., 1999). Intracellularly, vitamin C serves to maintain prosthetic ions in their reduced forms (e.g., Fe^{++}), scavenges free radicals to protect tissues from oxidative damage, and functions as a cofactor in a number of enzyme systems involved in the synthesis of collagen, microsomal drug metabolism, and the processing of certain neurotransmitters and peptide hormones (Marcus and Coulston, 1990; Tsukaguchi et al., 1999). As summarized by the National Research Council (1989), vitamin C is absorbed in the intestine by a sodium-dependent transport system and distributed to body tissues via blood as an unbound anion. From the blood, vitamin C is taken up by cells via a saturable, high affinity, sodium-dependent, transport system that results in intracellular vitamin C levels in the mM range. This transport system has been identified in a variety of cell types including leukocytes (Moser, 1987), endothelial cells (May and Qu, 2005), lung cells (Castranova et al., 1993), and Leydig cells (Moger, 1987).

Because intracellular levels are what matter, it is the kinetic parameters (e.g., Km, Vmax) of the vitamin C transport systems in marmosets and humans, not the absolute plasma levels, that will determine whether plasma vitamin C levels provide any protection from DEHP-induced testicular toxicity. While these kinetic differences are not known, evolutionary pressures typically result in enzyme systems that operate most efficiently under typical biological conditions, which may vary significantly among species. Thus, the average plasma vitamin C levels in marmosets (1.9 mg/dL) and humans (0.8 mg/dL) noted at required dietary levels for each species (NRC, 1989; Layne and Power, 2003) probably afford each a comparable degree of protection, if any. In other words, directly comparing plasma vitamin C levels across species is probably not a reliable indicator of the relative degree of protection those plasma levels might afford each species.

In summary, the need for supplemental vitamin C in primate and human diets reinforces the similarity between the two primate species. Since the amount of vitamin C administered in Tomonari et al. was in line with dietary recommendations, and since there is no reliable way to compare serum vitamin C levels across species, there is no reason to question the results of the study, and no reason to consider the results not relevant to assessing potential health effects in humans. The administration of medically appropriate amounts of vitamin C to the marmosets certainly would not appear to provide any scientific reason to prefer rodent data over the primate data for human hazard and risk assessment. Further, one might question whether it would have been scientifically appropriate, or even ethical, to withhold vitamin C from the marmosets.

Indeed, had vitamin C been withheld or administered in artificially low doses, interpretation of any adverse findings would be difficult at best.

D. Based on Pharmacokinetic Differences, Marmosets Are Less Susceptible Than Rodents to Developmental Toxicity from Phthalate Exposure

OEHHA Comment: "*In general, findings from [several studies cited by the Panel] clearly indicate that pharmacokinetic features of DEHP are qualitatively similar between marmosets and rats.*"

OEHHA concludes that data from several studies indicate that there are no DEHP pharmacokinetic differences between marmosets and rats, and that these studies do not support the Panel's statement in its earlier comments that "primates are less susceptible than rodents for developmental toxicity based on metabolism, absorption and elimination." On the contrary, several studies do support the conclusion that, based on pharmacokinetic differences, marmosets are less susceptible than rodents to developmental toxicity from phthalate exposure.

Rhodes et al. (1986) reported that marmosets dosed with dietary DEHP at 2,500 mg/kg/day achieved a maximum absorbed dose that was 10 to 25-fold lower than that of equally dosed rats. Similar results were obtained in studies in cynomologus monkeys (Astill, 1989). Both findings are supported by results of a recent study (Kurata et al., 2005) in which juvenile rats and marmosets were gavaged with 100 mg/kg DEHP. Plasma radioactivity measurements taken up to 24 hr post-dosing indicated that rats absorbed 20 to 100-fold more DEHP than marmosets. While this radiolabel study could not differentiate between DEHP and its metabolites, the results of Kessler et al. (2004) bear on this issue. In Kessler et al., pregnant and nonpregnant rats and marmosets were given oral doses of 30 or 500 mg/kg/day DEHP. In both species, MEHP was present in the blood at much higher levels than DEHP. In rats, the normalized areas under the concentration-time curves (AUCs) for MEHP were 100-fold higher than the normalized AUCs for DEHP; in marmosets, however, this difference was only about 10-fold. There was also a significant interspecies difference in plasma MEHP levels. Peak blood levels of MEHP in rats were 2 to 4-fold higher than those in marmosets, while AUC measurements indicated that MEHP levels in rats were 4 to 12-fold higher than those of marmosets. Thus, current evidence indicates that, when exposed to similar levels of DEHP, rats experience much higher levels of the toxicologically relevant metabolite, MEHP, than do marmosets. This indicates that marmosets, and other primates, are less susceptible than rodents to developmental toxicity from phthalate exposure based on pharmacokinetic differences.

II. THE MARMOSET DATA COMPRISE SCIENTIFICALLY VALID DATA, NOT CONSIDERED BY NTP-CERHR, WHICH ESTABLISH THAT THE PHTHALATES DO NOT MEET THE CRITERIA FOR LISTING UNDER PROPOSITION 65

As discussed above, OEHHA stated in its response to the Panel's earlier comments that the marmoset data in Tomonari et al. (2004) were "relevant for DBP, BBP, DnHP, and DIDP" and thus considered by OEHHA to be "'new data' that were not considered by the authoritative body." After acknowledging this fact, OEHHA rejected the marmoset data, stating that several of the marmoset's reproductive features make marmosets an unacceptable model for investigating developmental toxicity in humans. However, as the preceding section makes clear, OEHHA's rejection of the marmoset study is unfounded; the marmoset is a suitable model for investigating the potential developmental toxicity of phthalates to humans. Because the marmoset study provides new data that were not considered by the authoritative body, and those data clearly establish that the association between adverse reproductive effects in humans and the phthalates is not "biologically plausible," OEHHA's decision to list these phthalates fails to meet the listing requirements of Proposition 65.

Under Proposition 65 Section 12306(h), to list the phthalates OEHHA must first determine that an authoritative body has "formally identified" the phthalates as causing reproductive toxicity.[7] OEHHA must further determine that the studies considered by NTP-CERHR satisfy the Section 12306(g) criteria for "as causing reproductive toxicity."[8] According to regulations, a chemical is identified "as causing reproductive toxicity" when:

> (1) Studies in humans indicate that there is a causal relationship between the chemical and reproductive toxicity; or
>
> (2) Studies in experimental animals indicate that there are sufficient data, taking into account the adequacy of the experimental design and other parameters such as, but not limited to, route of administration, frequency and duration of exposure, numbers of test animals, choice of species, choice of dose levels, and consideration of maternal toxicity, indicating that an association between adverse reproductive effects in humans and the toxic agent in question is biologically plausible.[9]

NTP-CERHR has not concluded that studies in humans indicate a causal relationship between these phthalates and reproductive toxicity (the first criterion). Rather, as the OEHHA listing package recognizes, NTP-CERHR relied upon studies in rodents in reaching its ostensible conclusions. Therefore, in this case only Section 12306(g)(2) is relevant. As such, the phthalates should be listed only if the data from experimental animals indicate that an association between adverse reproductive effects and the phthalates is "biologically plausible."

Proposition 65 also contains a provision, Section 12306(h), which states:

> The lead agency [OEHHA] shall find that a chemical does not satisfy the definition of "as causing reproductive toxicity" if scientifically valid data which were not considered by the authoritative body clearly establish that the chemical does not meet the criteria of subsection (g), paragraph (1) or subsection (g), paragraph (2).[10]

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7 *See* CAL. CODE REGS. tit. 22, § 12306(d).

8 *See id. at* § 12306(g)(1)-(2).

9 *Id*.

10 *Id*. *at* 12306(h).

Thus, if scientifically valid data from experimental animals which were not considered by NTP-CERHR clearly establish that an association between adverse reproductive effects and the phthalates is not "biologically plausible," OEHHA must find that the phthalates do not satisfy the definition of "as causing reproductive toxicity." The marmoset data in Tomonari et al., which were acknowledged by OEHHA to be new data that were not considered by NTP-CERHR, clearly establish that an association between adverse reproductive effects and the phthalates is not "biologically plausible."

Tomonari et al. (2004; and MCSI, 2003) conducted a repeated oral dose study of the effects of DEHP treatment on the development of the male reproductive tract in common marmoset monkeys (*Callithrix jacchus*). The animals were administered 0, 100, 500 or 2500 mg/kg/day by gavage on a daily basis for 65 weeks, from weaning (about three months) until about 18 months of age. This exposure period covered the entire sexual maturation phase as marmosets reach sexual maturity at about 400 to 450 days (57-65 weeks). During the treatment period, the testosterone levels in all treated groups were similar to those of control groups. At the end of the treatment period, the animals were examined for gross and histologic evaluation of principal organs. The testes and accessory organs were subjected to light and electron microscopic examination, and measurements of hormone levels and sperm counts were carried out.

No treatment-related abnormalities were observed in microscopic and functional examinations of the marmosets' testes, and there were no treatment-related effects on sperm count. In addition, histochemical examination after 3β hydroxysteroid dehydrogenase staining did not reveal any alteration in steroid synthesis. The only significant effect observed, a dose-dependent increase in P450 content, was considered to be an adaptive change and not an adverse affect. Thus, this study demonstrated that daily administration of high doses of DEHP (up to 2,500 mg/kg/day) spanning the entire period of sexual maturation had no effect on male reproductive tract development in the marmoset.

Therefore, the empirical data from marmosets, which were shown in the preceding section to be valid for assessing human reproductive toxicity, indicate that primates are at least much less sensitive to the effects of phthalates than are rodents and may in fact be refractory, as there was no evidence of effects at the highest levels tested. A similar lack of effect was noted by Kurata et al. (1998) in adult marmosets treated with 2,500 mg/kg DEHP for 13 weeks, and by Pugh et al. (2000) in adolescent cynomolgus monkeys treated with 500 mg/kg DEHP for 14 days.

Humans are primates, and therefore data from primate studies are likely much more indicative of what effect can be anticipated in humans than data from rats. The recent marmoset data, along with the data of Kurata et al. and Pugh et al., demonstrate that an association between phthalates and adverse reproductive effects in humans is not biologically plausible. Thus, scientifically valid data from experimental animals which were not considered by NTP-CERHR clearly establish that of the criteria for "as causing reproductive toxicity" are not met. Therefore, the phthalates fail to meet the Proposition 65 listing criteria.

III. NTP-CERHR FOUND MINIMAL TO NEGLIGIBLE RISK OF HUMAN REPRODUCTIVE TOXICITY FOR THESE PHTHALATES; THEREFORE THE PROPOSITION 65 LISTING CRITERIA ARE NOT MET

OEHHA's stated basis for listing these phthalates is the monographs published in 2003 by NTP-CERHR. (NTP-CERHR, 2003a,b,c,d). However, in representing NTP-CERHR's conclusions in these monographs, OEHHA fails to acknowledge qualifying language, which results in an overstatement of NTP-CERHR's findings of phthalate toxicity. For example, for DBP, BBP and DIDP, respectively, NTP-CERHR stated:

> In this case, recognizing the lack of human data and the clear evidence of effects in laboratory animals . . ., the NTP judges the scientific evidence sufficient to conclude that DBP may adversely affect human reproduction or development *if exposures are sufficiently high*.

(NTP-CERHR, 2003b, emphasis added); and

> The NTP believes it is reasonable and prudent to conclude that the results reported in laboratory animals indicate a potential for similar or other adverse effects in human populations *if exposures are sufficiently high.*

(NTP-CERHR, 2003a, emphasis added); and

> In this case, recognizing the lack of human data and the evidence of effects in laboratory animals, the NTP judges the scientific evidence sufficient to conclude that DIDP is a developmental toxicant and could adversely affect human development *if the levels of exposure were sufficiently high.*

(NTP-CERHR, 2003d, emphasis added).

Thus, for each case in which NTP-CERHR made a determination of concern about a phthalate's potential reproductive or developmental toxicity (it made no concern determination for DnHP), it qualified its determination by indicating the potential for toxicity only at "sufficiently high" exposure levels. Because of these qualifications, NTP-CERHR's findings of potential toxicity are inextricably tied to exposure levels, which, as explained at length by the Panel in its earlier comments (Section III, Table 1), are not "sufficiently high" to indicate a potential for human effects. OEHHA fails to acknowledge the significance of NTP-CERHR's use of this qualifying language.

In addition to failing to acknowledge language linking risk to exposure, OEHHA ignores the fact that NTP-CERHR found minimal or negligible concern for human developmental or reproductive toxicity for DBP, BBP and DIDP. About DBP, NTP-CERHR stated:

> The NTP concurs with the CERHR Phthalates Expert Panel that there is *minimal concern for developmental effects* when pregnant

women are exposed to DBP levels estimated by the Panel (2-10 μg/kg bw/day);[11]

and

"The NTP concurs with the CERHR Phthalates Expert Panel that there is *negligible concern for reproductive toxicity* in exposed adults.

(NTP-CERHR, 2003b, emphasis added).

About BBP, NTP-CERHR stated:

The NTP concludes that there is *minimal concern for developmental effects* in fetuses and children;

and

The NTP concurs with the CERHR Phthalates Expert Panel that there is *negligible concern for adverse reproductive effects* in exposed men.

(NTP-CERHR, 2003a, emphasis added).

About DIDP, NTP-CERHR stated:

"The NTP concurs with the CERHR Phthalates Expert Panel that there is *minimal concern for developmental effects* in fetuses and children ;

and

"The NTP concurs with the CERHR Expert Panel that there is *negligible concern for reproductive toxicity* in exposed adults (emphasis added).

(NTP-CERHR, 2003d, emphasis added).[12]

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11 Based upon estimated DBP exposures among some women of reproductive age, the NTP did have "some concern" for DBP causing adverse effects to development to fetus of women so exposed. However, the exposure estimates causing "some concern" were based on preliminary urinary metabolite data from the CDC for a small, nonrepresentative sample of women (Blount et al., 2000; Kohn et al., 2000). CDC scientists subsequently analyzed data for women of childbearing age in a much larger and statistically representative sample (Manori et al., 2004). Those results showed that women of reproductive age had DBP exposure levels the same as or lower than other age groups of women.

Moreover, regarding the toxicity of DnHP, NTP-CERHR stated:

> The NTP judges the scientific evidence insufficient to reach a conclusion regarding the potential for DnHP to adversely affect human development or reproduction.

(NTP-CERHR, 2003c). Because NTP-CERHR reached no conclusion with regard to the potential of DnHP to adversely affect human reproduction or development, OEHHA's justified its listing decision by relying on "the generally accepted assumption that 'an agent that produces an adverse developmental effect in experimental animal studies will potentially pose a hazard to humans *following sufficient exposure during development* . . . .'" (citing EPA, 1991, emphasis added). In so doing, OEHHA both ignores the authoritative body's explicit failure to conclude that DnHP adversely affects human development or reproduction and, again, fails to acknowledge qualifying language necessarily linking adverse affects to "sufficient exposure." Therefore, even more so than for DBP, BBP and DIDP, OEHHA relies on an overstatement of the authoritative body's assessment of DnHP's toxicity to justify its listing.

These statements by NTP-CERHR do not satisfy the prong of the first regulatory criterion that the authoritative body's report must "conclude[] that the chemical causes reproductive toxicity" because for purposes of Proposition 65, the reproductive toxicity must plausibly be in humans.[13] As discussed in Section II of these comments, the Proposition 65 regulations define a conclusion of "as causing reproductive toxicity" as one that satisfies the requirement that studies in experimental animals indicate that there are sufficient data to show that an association between adverse reproductive effects in humans and exposure to the chemical in question is "biologically plausible."[14] NTP-CERHR does not "conclude" that the phthalates cause reproductive toxicity in humans under this definition. Instead, their statements conclude only that such effects occur in rodents. There is no finding that an association between the phthalates and adverse reproductive effects is biologically plausible. As such, the suggestion to treat the phthalates as potentially reproductively toxic in humans is merely a default assumption, not a conclusion of biological plausibility.

As a result, OEHHA's decision to list these four phthalates under Proposition 65 is based on its incomplete, and therefore overstated, representation of NTP-CERHR's conclusions as to the phthalates' potential toxicity. NTP-CERHR found only that these phthalates have the "potential" to adversely affect humans if concentrations are "sufficiently high," and stated that it had minimal or negligible concern for developmental or reproductive effects in humans. By

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12 The NTP-CERHR stated that "[t]hese conclusions are based on the assumption that the general US population is exposed to DIDP at less than 30 µg/kg bw/day." In its August 2004 comments, the Panel explained that, based on analogy to DINP exposures, urinary metabolite data indicated that the best estimate for ambient exposure to DIDP is ≤ 1 µg/kg/day (McKee et al., 2004). This exceedingly low exposure level is supported by another study which found that urinary levels of DIDP following exposure from the use of personal hygiene products were below detectable limits. (Stock et al., 2001; Stock personal communication). Thus, the NTP-CERHR's overall conclusions of minimal to negligible concern from DIDP exposures are well supported.

13 *See* CAL. CODE REGS. tit. 22, § 12306(d)(1).

14 *Id.* at § 12306(g)(2).

leaving out this language, OEHHA changes fundamentally the nature of NTP-CERHR's conclusions. Because NTP-CERHR did not conclude that the phthalates cause reproductive toxicity, the Proposition 65 listing criteria are not met for these four phthalates.

IV. OEHHA HAS NO STATUTORY MANDATE TO LIST CHEMICALS SUCH AS THESE PHTHALATES, WHICH POSE NO SIGNIFICANT RISK TO HUMAN HEALTH; THEREFORE, LISTING OF THESE PHTHALATES MAKES LITTLE SENSE FROM A PUBLIC POLICY PERSPECTIVE

As stated in its August 2004 comments, the Panel believes it makes little sense to list these phthalates under Proposition 65, as it would be poor public policy to list chemicals for which the data clearly demonstrate no significant risk to public health. The Panel's earlier comments demonstrated that low risk by showing that exposures to phthalates from all sources are well below what are likely to be Maximum Allowable Dose Levels (MADLs) for DBP, BBP, DnHP and DIDP. OEHHA's response to those comments states that OEHHA has not calculated MADLs for these chemicals and so has no basis to agree or disagree with the Panel's comment. This is a somewhat disingenuous response. The procedure for calculating a MADL is straightforward – select the most sensitive relevant study of sufficient quality, divide its no observed effect level by 1000, and multiply by either 70 or 58 kilograms, depending on whether the applicable reproductive effect is upon the male or upon the female or conceptus.[15] This is precisely what the Panel did to generate likely MADL values. The Panel knows of no study OEHHA could select that would give a substantially lower MADL value. However, even if OEHHA were to calculate MADLs an order of magnitude below those calculated by the Panel, average exposures to the phthalates – from all sources – would still be well below the MADL. The Panel's primary point, therefore, remains valid: the risks from phthalates are so low that it is highly unlikely that a Proposition 65 warning would be necessary for any product containing these phthalates.

OEHHA also states that the question of whether exposures are below the MADL has no bearing on an authoritative bodies listing – that it is a question for consideration when and if the phthalates are listed. The Panel disagrees. There is no statutory mandate that OEHHA list each and every substance which an authoritative body has concluded to cause reproductive toxicity in animals. The statute states:

> On or before March 1, 1987, the Governor shall cause to be published a list of those chemicals known to the state to cause cancer or reproductive toxicity within the meaning of this chapter, and he shall cause such list to be revised and republished *in light of additional knowledge at least once per year thereafter*. (CAL. HEALTH & SAFETY CODE § 25249.8, emphasis added)

Part of the additional knowledge OEHHA could apply is knowledge that a given chemical is unlikely ever to pose a risk to human reproduction due the large gap between effect levels in test animals and human exposures. In addition, as discussed in Section III of these comments, the very authoritative body on which OEHHA relies for its proposed listings of DBP, BBP, DnHP and DIDP has found minimal to negligible concern that these phthalates will cause reproductive

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15 *See* CAL. CODE REGS. tit. 22, § 12803.

effects in humans. In such a case, the Panel believes that good policy judgment dictates that the chemicals not be listed.

OEHHA, in its response to the Panel's earlier comments, describes Proposition 65 as a "public right-to-know statute" and an "informational resource" for the public about chemicals "known to cause reproductive toxicity." Yet, as discussed at length in the Panel's earlier comments, and expanded upon here, the toxicity and exposure data indicate it is highly unlikely that human exposures to these phthalates will in fact cause such effects. Thus, rather than the Proposition 65 list serving as a reliable "informational resource" about risks from phthalates, it would be misleading with respect to these substances.

Moreover, inclusion of chemicals on the Proposition 65 list inevitably leads to public and regulatory concern about the chemicals thus listed. As a result, even though a company's product may result in phthalate exposures below the maximum allowable dose level, exempting the product from warning requirements, [16] the stigma associated with using a chemical listed as "known to the State" to cause reproductive/developmental toxicity often forces companies to eliminate use of the listed chemical. Yet, where a chemical is well studied, such that its risks are well characterized, as for phthalates, use of an unlisted substitute chemical will not necessarily result in a public health benefit. The substitute may be unlisted because it is not as well-studied, so that its own hazards have not yet been discovered. It makes little sense to drive companies to make such a substitution where the data show that risks from the chemical are extremely low, as is the case for the phthalates.

The use of a given chemical in products results from a balancing of safety, performance and cost. Reformulation away from the chemical is likely to cause degradation in at least one of those factors. The Panel strongly reiterates that sound public policy would avoid promoting such consequences through Proposition 65 listing, where human exposures to substances – such as DBP, BBP DnHP and DIDP – have been shown to pose a very low risk of reproductive or developmental toxicity.

CONCLUSION

The data presented in the Panel's earlier comments, and expanded upon here, support a conclusion that DBP, BBP, DnHP and DIDP do not pose a significant risk of reproductive or developmental toxicity in humans. The recent marmoset data and NTP-CERHR's statements demonstrate that the Proposition 65 listing criteria are not met for these four phthalates. Further, it would not be good public policy to list such low-risk chemicals. The Panel therefore believes that OEHHA should not list these phthalates under Proposition 65.

[16] See CAL. HEALTH & SAFETY CODE § 25249.10(c); 22 CCR. § 12801.

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